Remarks

Applicant appreciates the Examiner's withdrawal of the rejections under 35 U.S.C.§§ 101 and 112, second paragraph.

The Amendments

Claim 1 has been amended to recite an isolated and purified polypeptide that has "at least 90% amino acid sequence identity" with SEQ ID NO:2. New claims that depend from claim 1 recite that the polypeptides have at least 95% (claim 44) or at least 99% (claim 45) amino acid sequence identity with the amino acid sequence of SEQ ID NO:2. Such polypeptides are taught at page 4, lines 7-12: "The present invention is, however, not limited to a Δ^6 desaturase having the sequence shown in Figure 1 (SEQ ID NO:2). . . . Sequence identities of at least 90%, at least 95% or at least 99% are most preferred."

Claims 14 and 42 have been amended to recite a moiety "capable of being isolated by affinity chromatography." Such moieties are taught at page 6, lines 23-24: "Another example of the provision of an additional sequence is where a polypeptide is linked to a moiety capable of being isolated by affinity chromatography."

New claim 46 recites an isolated and purified polypeptide having desaturase activity which comprises a part of the amino acid sequence as shown in SEQ ID NO:2. Claim 13 supports new claim 46. Claim 13 recites a polynucleotide consisting of SEQ ID NO:2 or "a part thereof."

None of these amendments introduces new matter.

The Objection to Claim 8

Claim 8 is objected to as not reciting words indicated by the acronym "GLA." Claim 8 has been canceled.

Applicant respectfully requests withdrawal of this objection

The Rejection of Claims 14, 23, and 42 Under 35 U.S.C. § 112, Second Paragraph

Claims 14, 23, and 42 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claim 23 has been canceled. Applicant respectfully traverses the rejection of claims 14 and 42.

The Office Action asserts that claims 14 and 42 are indefinite because the scope of "moiety" is unclear. Paper 17, page 2, line 21 to page 3, line 2. Claims 14 and 42 have been amended to recite a "moiety capable of being isolated by affinity chromatography" in place of "moiety." Such moieties were well known when the application was filed and would be recognized by those skilled in the art. In addition, the specification teaches that, "The moiety may be an epitope and the affinity column may comprise immobilized antibodies or immobilised antibody fragments that bind to said epitope." Page 6, lines 24-26. Thus the scope of the recited moiety is clear.

Applicant respectfully requests withdrawal of this rejection.

The Rejection of Claims 1-12, 14, and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 1-12, 14, and 23 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that was not sufficiently described in the specification. Claims 8-11 and 23 have been canceled. Applicant respectfully traverses the rejection of claims 1-7, 12, and 14.

To satisfy the written description requirement, the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d. 1555, 1563-1564 (Fed. Cir. 1991). The Office Action asserts that claims 1-7, 12, and 14 are directed to a genus of polypeptides and that the specification does not describe modified polypeptides encompassed by the claims. Paper 17, page 3, line 24 to page 4, line 3.

The written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (January 5, 2001); approved in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). The specification meets this standard because the specification describes the recited genus by both structure and chemical properties.

As recited in independent claim 1, polypeptides of the genus have desaturase activity, which is a chemical property. The specification discloses at page 4, line 24 that "a polypeptide of the present invention has desaturase activity." Polypeptides of claim 1 also comprise one or more amino acid deletions, insertions, or substitutions relative to SEQ ID NO:2 and are at least 90% identical to SEQ ID NO:2; these are structural properties. The specification provides the amino acid sequence shown in SEQ ID NO:2. The specification also discloses that the invention encompasses polypeptides having amino acid sequences that are at least 90% identical to SEQ ID NO:2: "The present invention is, however, not limited to a Δ^6 desaturase having the sequence

shown in Figure 1 (SEQ ID NO:2). . . . Sequence identities of at least 90%, at least 95% or at least 99% are most preferred." Page 4, lines 7-12. Thus, the specification describes the polypeptides of claim 1 in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of this genus of polypeptides when the application was filed.

The specification also adequately describes the polypeptides of dependent claims 2-7, 12, and 14. Claim 2 recites polypeptides that have a cytochrome domain in addition to the characteristics recited in claim 1. The Office Action asserts, however, that claim 2 is not adequately described because the specification "fails to present any identifying characteristics of any domain of any cytochrome other than the described domain of cytochrome b5." Paper 17, page 5, lines 9-10. The specification defines a cytochrome domain as "an electron-transporting domain that contains a heme prosthetic group." Page 5, lines 11-12. Thus the specification describes the polypeptides of claim 2 as including functional (electron transport activity) and chemical (a heme group) properties. As evidenced by the attached references, cytochrome domains were known in the art prior to the November 24, 1997 effective filing date of the application:

- Myllykallio *et al.* (*J. Bacteriology* (April 1997) *179*:2623-2631; Exhibit A) teaches mitochondrial *c*-type cytochrome domains and characteristics of these domains. Myllykallio teaches the amino acid sequence of a mitochondrial *c*-type cytochrome domain of a cytochrome c_y protein. See Figure 2. Myllykallio also teaches that mitochondrial class I *c*-type cytochrome domains have a characteristic "Cys-Xaa-Yaa-Cys-His heme-binding motif and a distal methionine residue as the sixth ligand of the heme iron." Page 2627, column 2, line 11 to page 2628, column 1, line 1, citation omitted.
- Stapleton *et al.* (*J. Biol. Chem.* (1995) *270*:29739-29745; Exhibit B) teaches

sequences characteristics of cytochrome P450 domains. Stapleton teaches that cytochrome P450 domains contain a "highly conserved motif, F*XX*G*XXX*C*X*G(*XXX*A), present in 202 of the 205 compiled [P450] sequences, thought to represent the heme binding site with the arrangement of amino acids around the cysteine residue postulated to preserve the three-dimensional structure of this region for ligand binding." Page 29743, column 1, lines 7-12, citations omitted.

- Bruschi *et al.* (*Biochemistry* (1992) *31*:3281-3288; Exhibit C) teaches the characteristics of cytochrome c3 domains were also known at the time the application was filed. Bruschi teaches identification of three cytochrome c3 domains in multiheme cytochrome c (Hmc) protein of *Desulfovibrio desulfuricans* G200. "A comparison of the arrangement of heme binding sites and coordinated histidines in the amino acid sequence of the cytochrome c3 and Hmc has shown that the latter contains four domains, three of which are complete c3-like domains. Lines 16-19 of the Abstract.

Thus, cytochrome domains were known in the art at the time of the effective filing date of the application and thus need not be disclosed in the application.

Claim 3 further recites that the polypeptide has a cytochrome b_5 domain. The specification discloses that such a domain "includes a H-P-G-G-X_{15}-F-X_{3-6}-H (SEQ ID NO:3), where X is any amino acid, motif." Page 5, lines 13-14. The attached references provide further evidence that cytochrome b_5 domains were known in the art prior to the November 24, 1997 effective filing date of the application:

- Sayanjova *et al.* (*Proc. Natl. Acad. Sci.* (1997) *94*:4211-4216; Exhibit D) teaches the amino acid sequence of borage (Bocytb5), rice (Oscytb5), and tobacco (ntcytb5) microsomal cytochrome b_5 proteins. See Figure 2.
- Mitchell *et al.* (*J. Biol. Chem.* (November 7, 1997) *272*:28281-28288; Exhibit E)

teaches the amino acid sequence of *S. cerevisiae* microsomal cytochrome b_5, and the amino acid sequence of cytochrome b_5 domains of *S cerevisiae* proteins *OLE1*, cytochrome b_2, and YMR272C. See Figure 1.

- Mitchell *et al.* (*J. Biol. Chem.* (1995) *270*:29766-29772; Exhibit F) teaches the amino acid sequence of rat, rabbit, human, bovine, rice, tobacco, brassica, yeast, *OLE1* protein cytochrome b_5 proteins. See Figure 7.

Thus cytochrome b_5 domains were both described in the specification and known in the art as of the filing of the application.

Claim 4 recites that the polypeptide has at least one histidine box. Claim 5 recites that the polypeptide has at least three histidine boxes. The specification describes a histidine box as containing an amino acid sequence Q-X-X-H-H. Page 18, line 23. The specification also discloses that a histidine box "may have an H-Q substitution." Page 5, line 21. Thus the specification discloses additional, distinguishing structural characteristics of the polypeptide of claims 4 and 5. The Office Action asserts that claim 5 lacks adequate written description because "the [de]saturase of SEQ ID NO:2, has only two histidine boxes as marked in Fig. 1." Paper 17, page 14-15. The specification does disclose, however, the amino acid sequence of histidine boxes, "H-X-X-H-H" and "Q-X-X-H-H." One of skill in the art could readily make and use a polypeptide having a third histidine box based on the disclosed amino acid sequence of SEQ ID NO:2.

The specification further describes the polypeptides of claims 6 and 7 by functional properties. Claim 6 recites that the polypeptide having desaturase activity is a front-end desaturase. The specification discloses that "'front-end' desaturation can [be] defined as the final desaturation on the fatty acid chain, usually introducing double bonds between a pre-

existing bond and the Δ-end of the carboxy group." Page 23, line 28 to page 24, line 2. Claim 7 recites that the polypeptide with desaturase activity is a Δ^6 desaturase. These polypeptides desaturate at the Δ^6 position of fatty acids. Page 2, lines 2-5.

The specification also describes the polypeptide of claim 12. Claim 12 recites a polypeptide of claim 1 that occurs naturally in *C. elegans*. The polypeptide of SEQ ID NO:2 is one such polypeptide. Thus the specification describes identifying characteristics of a representative polypeptide of claim 12.

The specification also describes the polypeptide of claim 14 by functional properties. Claim 14 recites a polynucleotide of claim 1 that comprises another moiety capable of being isolated by affinity chromatography. The specification provides an example of moieties capable of being isolated by affinity chromatography. The specification discloses that the "moiety may be an epitope and the affinity column may comprise immobilised antibodies or immobilised antibody fragments that bind to said epitope." Page 6, lines 24-26.

The specification adequately describes the polypeptides recited in the rejected claims. Applicant respectfully requests withdrawal of this rejection of claims 1-7, 12 and 14.

The Rejection of Claims 1-12, 14 and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 1-12, 14, and 23 are rejected under 35 U.S.C. § 112, first paragraph as not being enabled for their full scope. Claims 8-11 and 23 have been canceled. Applicant respectfully traverses the rejection of claims 1-7, 12, and 14.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). That some

experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The test is not merely quantitative, because a considerable amount of experimentation is permissible if the experimentation is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The present specification and the level of skill in the art provide the skilled practitioner with sufficient guidance to practice the claimed invention without having to resort to undue experimentation.

The Office Action asserts that the claims are not enabled because they are directed to a large genus of polypeptides having desaturase activity. Paper 17, page 7, lines 15-17. The Office Action further asserts, "Although the methods of gene cloning and manipulation are well developed and skills of artisans are high, it is not a routine in the art to clone all possible desaturases from all natural or man made sources and selected those that are at least 50% identical to SEQ ID NO:2. Also, it is not routine experimentation in the art to modify SEQ ID NO:2 by making deletions, insertions and substitutions resulting in a protein that has 50% identity to SEQ ID NO:2 and desaturase activity." Paper 17, page 8, lines 4-9.

Claim 1, the only independent claim of the rejected claim set, has been amended to recite desaturase polypeptides comprise one or more amino acid deletions, insertions or substitutions relative to SEQ ID NO:2 and are at least 90% amino acid sequence identity with SEQ ID NO:2. One of skill in the art, using the teaching of the specification could make and use the claimed polypeptides.

As acknowledged in the Office Action, methods of gene cloning and manipulation are

well developed and the level of skill in this art is high. *Id.* Given the knowledge in the art and the level of skill in the art, any experimentation needed to prepare the claimed desaturase polypeptides would merely involve the practice of routine methods. Using the teachings of the specification, one skilled in the art could test polypeptides comprising one or more the amino acid insertions, deletions, or substitutions relative to SEQ ID NO:2 but having at least 90% amino acid sequence identity to SEQ ID NO:2 without having to resort to undue experimentation. The specification teaches how to do such tests at page 22, lines 1-12 and page 23, lines 2-6. The specification teaches that fatty acid profiles of cells containing the coding sequence for a desaturase can be separated by gas chromatography. Analysis of the profiles of the fatty acids determines the presence of a product of a desaturase and identifies the polypeptide as a desaturase. Gas chromatography is a technique that was well known in the art at the time the application was filed. One of skill in the art, using routine methods of gene cloning and manipulation, would be able to produce the polypeptides recited in claim 1. One of skill in the art, using routine methods of gas chromatography, would then be able to test the polypeptides for desaturase activity. Practice of these routine methods does not constitute undue experimentation.

The Office Action also asserts that the specification does not provide sufficient guidance "as to the rules for performing substitutions, deletions or insertions without [having] an adverse effect on protein function." Paper 17, page 8, lines 22-24. The level of skill in the art at the time the application was filed, however, was such that deletions in the amino acid sequence of SEQ ID NO:2 could have been made without undue experimentation. The Patent Office acknowledges that, with respect to claim 13, applicants demonstrated that one of skill in the art could make deletions in the desaturase polypeptide of SEQ ID NO:2 and that claim 13 is

enabled. Thus polypeptides having deletions relative to SEQ ID NO:2 as recited in claims 1-12, 14, and 23 are enabled.

The specification also enables polypeptides having amino acid insertions relative to SEQ ID NO:2. The specification teaches that "[a]mino acid insertions . . . may be done to alter the nature of the polypeptide (e.g. to assist in identification, purification or expression)." Page 8, lines 10-12. These insertions may alter the polypeptide to "provide some protection against proteolytic cleavage." Page 6, lines 17-18. Other insertions can be, for example, "a signal sequence . . . to direct the transport of the polypeptide to a particular location within a cell or to export the polypeptide to a particular location within a cell or to export the polypeptide from the cell." Page 6, lines 20-22. The specification also teaches that insertions can be "moiet[ies] capable of being isolated by affinity chromatography." Page 6, line 23. Amino acids and amino acid sequences that perform these functions were well known in the art prior to the effective filing date of the application. Thus, the specification teaches how to make amino acid insertions relative to SEQ ID NO:2. Any experimentation undertaken to produce such polypeptides would be merely be routine to those of skill in the art, not undue.

Polypeptides containing substitutions with respect to SEQ ID NO:2 also are enabled. The specification discloses examples of amino acid residues that can be substituted for other amino acid residues "without eliminating a desired property of that polypeptide (such as desaturase activity)." Page 7, lines 19-20. See page 7, line 21 to page 8, line 2 for examples of amino acid substitutions. The specification also provides guidance as to which amino acid residues of SEQ ID NO:2 should most likely <u>not</u> be substituted with other amino acid residues to produce a polypeptide with desaturase activity. For example, the specification discloses that polypeptides

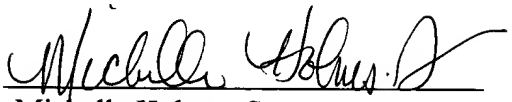
that have desaturase activity comprise particular conserved domains. One of skill in the art would have understood that conserved domains of proteins are typically not mutated if enzymatic activity of a polypeptide is to be maintained. The specification discloses that these domains include histidine boxes, "H-X-X-H-H," and variant histidine boxes, "Q-X-X-H-H." Page 5, lines 20-21 and page 2, lines 25-27. The amino acid sequence of SEQ ID NO:2 contains a histidine box at amino acid residues 205-209. The specification also discloses that SEQ ID NO:2 contains a variant histidine box and that in Figure 1 the amino acid residues of "the variant third histidine box are underlined." Page 18, lines 4-5. The specification further discloses a third conserved motif, a cytochrome b_5 motif, in the polypeptide of SEQ ID NO:2. "Note the presence of the H-P-G-G cytochrome b_5 motif in the N-terminus (encoded by bases 96-108)" of SEQ ID NO:2, underlined in Figure 1. Page 20, lines 27-28. One of skill in the art would realize that amino acid substitutions in these regions likely should not be substituted with other amino acid residues.

Using the guidance provided by the specification, one of skill in the art would have been able to produce a polypeptide that has amino acid substitutions relative to SEQ ID NO:2, shares at least 90% amino acid sequence identity with SEQ ID NO:2, and has desaturase activity. Any experimentation involved in producing and testing these polypeptides would have been routine to those of skill in the art and not undue.

Applicant respectfully requests withdrawal of this rejection of claims 1-7, 12, and 14.

Respectfully submitted,

Date: November 10, 2003

By: 
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